White matter integrity in brain networks relevant to anxiety and depression: evidence from the Human Connectome Project dataset

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Abstract

Anxiety and depression not only exert a critical influence on localized brain regions involved in affective processing but also affect the communication within global brain networks and between these networks and the amygdala. Functional connectivity studies support the effect of anxiety and depression on four critical brain networks involved in top-down attention control (fronto-parietal network; FPN), salience detection and error monitoring (cingulo-opercular network; CON), bottom-up stimulus-driven attention (ventral attention network; VAN), and default mode (default mode network; DMN). However, structural evidence on the white matter (WM) connections within these networks and between these networks and the amygdala is lacking. The current study in a large healthy sample (n = 483) observed that higher trait anxiety-depression predicted lower WM integrity in the connections between amygdala and specific regions of the FPN, CON, VAN, and DMN. We discuss the possible consequences of these anatomical alterations for cognitive-affective functioning and underscore the need for further theory-driven research on individual differences in anxiety and depression on brain structure.

Keywords: diffusion tensor imaging; structural MRI; anxiety; depression; human connectome project; HCP

Background

Affective disorders not only affect localized brain regions involved in the processing of emotions but are also associated with altered communication within global brain networks and broad cognitive function. Notably, anxiety is presumed to impact four core brain networks involved in cognitive function, specifically the fronto-parietal network (FPN), cingulo-opercular network (CON), ventral attention network (VAN), and default mode network (DMN) (Sylvester et al. 2012; Liao et al. 2010a). Additionally, anxiety perturbs functional connectivity between the amygdala and key regions of these four networks at rest (Etkin et al. 2009), during emotion regulation (Etkin et al. 2010) and to masked threats (Monk et al. 2008). Similar deficits in network connectivity have been reported in depression (Sylvester et al. 2012; Cullen et al. 2014; Lu et al. 2012). Interestingly, it has been hypothesized that anxiety and depression are associated with overactivation of the CON and VAN (in case of anxiety) but underactivation of the FPN and DMN (Sylvester et al. 2012). However, structural evidence on greater or reduced integrity of brain white matter supporting such hypotheses is limited.

Sylvester et al. (2012) hypothesize that anxiety disorders are characterized by perturbed functional activity and connectivity in four important general neural networks (for the specific regions involved in each network please see Table 1). The CON, or salience network, is responsible for detecting errors and conflicts, although the dorsal anterior cingulate cortex of this network has also been reported to be involved in affect processing and cognitive control (Sylvester et al. 2012). The FPN is principally involved in the exertion of top-down cognitive control (Dosenbach et al. 2008) as opposed to the VAN, which supports bottom-up stimulus-driven attention (Fox et al. 2006). In contrast to the other networks, which are hypothesized to

operate bilaterally, the VAN is postulated to be predominantly right-lateralized (Fox et al. 2006). Finally, the DMN is involved in a broad array of functions such as future planning, self-referential activities, and emotion regulation (Raichle et al. 2001). Although functional connectivity is variable over time (Honey et al. 2009), it is constrained by the anatomical white matter (WM) structure in the brain (Honey et al. 2009; Diez et al. 2015). Patterns in resting state activity in DMN and FPN have been linked to anatomical connectivity patterns, showing for example strong interconnections (i.e., connection density) between the precuneus and medial prefrontal cortex (PFC) of the DMN (Honey et al. 2009). Current evidence on the connectivity between the key regions of the networks (Table 1) and the amygdala is limited. Although the amygdala has been a main point of interest in research for the past number of years due to its prominent role in anxiety and depression (e.g., Beesdo et al., 2009; Rauch, Shin, & Wright, 2003), research on the connectivity between the amygdala and other parts of the brain has been more limited (e.g., Kim & Whalen, 2009; Tromp et al., 2012; Taylor et al., 2007). While connectivity studies have been increasing recently, they have, to date, only examined the connectivity between the amygdala and one other brain region or network. For instance, studies in trait anxiety (Kim and Whalen 2009), generalized anxiety disorder (Tromp et al. 2012), and major depression (Taylor et al. 2007; Liu et al. 2016) suggest that increased symptoms of affective disorders are associated with lower WM integrity (lower fractional anisotropy, FA) in the amygdala – PFC tracts (including regions of the CON, VAN, and DMN). However, opposite findings have found positive associations between FA values and trait anxiety in ventrolateral PFC of the VAN (Clewett et al. 2014) or uncinate fasciculus connection with PFC (Modi et al. 2013). Discrepant findings are also present in other WM regions of the brain (e.g., Ayling et

al. (2012) for a review) and could be due to small sample sizes, dissimilar definitions of regions of interest, differences in clinical status of participants, or the use of different methods for the measurement of tract integrity. Taken together, the limited research available on the influence of affective disorders on structural WM integrity is contradictory and has insufficiently taken into account the relevant brain networks *per se*. Research on the influence of anxiety and depression on brain anatomy would greatly benefit from large-scale theory-driven studies using robust methods for the calculation of white matter integrity.

Therefore, this study aimed to investigate the extent to which trait anxiety and depression has an impact on the WM integrity of four critical brain networks involved in the top-down control of attention (FPN), error monitoring (CON), stimulus-driven attention (right-lateralized VAN), and default-mode and emotion regulation (DMN) and their relation to the amygdala using a comparatively large representative sample (the Human Connectome Project, HCP). Based on prior theoretical models (Sylvester et al. 2012), we anticipated 1) that more anxiety-depression would predict greater structural connectivity in the amygdala-FPN and amygdala-VAN paths but less structural connectivity in amygdala-CON and amygdala-DMN paths. Moreover, also based on prior work (Sylvester et al. 2012; Liao et al. 2010a), we hypothesized that 2) overactivation of CON and VAN in anxiety and depression would be associated with greater structural connectivity within structures of these networks whereas the underactivation of DMN and CON previously reported in relation to these disorders led us to expect reduced structural connectivity among the individual network structures.

Methods

Sample

The present study sample consisted of the HCP (S500 release) data. This release contained 543 participants of which 483 subjects (286 females) aged between 22 and 36 (*M* = 29.16; *SD* =3.46; Table 2) could be used for analysis in the current study. A total of 60 HCP participants could not be included in this study due to missing or invalid diffusion data (n = 56), no Achenbach adult self-report scores (n = 3), or incomplete ethnicity data (n = 1). Relevant sample characteristics are presented in table 2. For estimate IQ, Ravens progressive matrices correct score was used (Raven et al. 2003). While the majority of the sample had a white ethnic background (n = 356; 50 Hispanic), participants of African American (n = 102), Asian or pacific (n = 9), and mixed (n = 6) or unknown (n = 10) ethnic background were also included. All data was handled in accordance with the HCP data use terms.

Achenbach adult self-report

The scale within the HCP that measures socio-emotional problems in the past six months is the Achenbach adult self-report (ASR; Achenbach 2009). Due to its large sample size, no diagnostic interview was available within this dataset. This self-report scale allows for the calculation an anxiety-depression scale (range 0-36 points). While there was unfortunately no appropriate scale measuring anxiety and depression separately, these are highly comorbid disorders that appear to share a lot of underlying features, including network dysfunction (Sylvester et al. 2012; Korgaonkar et al. 2014). The presence of high comorbidity is supported by the significant correlation between the DSM depression and DSM anxiety measures ($r(481) = .67$, $p < .001$) in the ASR in this sample. Mean ASR anxiety-depression score in this sample was 5.64 (SD =5.33; Table 2) and only a small subsample

suffered from anxiety or depression symptoms that reached clinical significance (14 participants or 2.90 % of the sample when using a cut-off of percentile 98). There was no gender difference in ASR anxiety-depression score ($t(481) = 0.56$, $p = .58$) .

MRI acquisition

All subjects were scanned at Washington University in St. Louis using a Siemens Skyra 3T scanner with a customized SC72 gradient insert (i.e., the 'Connectome Skyra' which improves the quality of the diffusion imaging scans). High angular diffusion MRI was recorded (spin-echo EPI sequence, repetition time (TR) = 5520 ms, echo time (TE) = 89.5 ms, flip angle = 78°, refocusing flip angle = 160°, field of view (FOV) = 210 x 180 (RO x PE), matrix = 168 x 144 (RO x PE), slice thickness = 1.25 mm, 111 slices, 1.25 mm isotropic voxels, multiband factor = 3, echo spacing = 0.78 ms, bandwith = 1488 Hz/Px, phase partial Fourier = 6/8, and b-values of 1000, 2000, and 3000 s/mm²). SENSE was used for diffusion reconstruction (Sotiropoulos et al. 2013). The dMRI protocol was completed in 6 runs, with 3 gradient tables (with 90 directions and 6 B0 acquisitions) applied in both right to left and left to right phase encoding. A T1w structural image (TR = 2400 ms, TE = 2.14 ms, TI = 1000 ms, flip angle = 8°, FOV = 224x224) sampled at the same resolution as the diffusion data was also included.

Regions of interest

The key brain regions of the networks of interest (i.e., FPN, CON, VAN, and DMN) will be used as seeds and targets in the subsequent analyses (Table 1). Since it was not feasible to manually draw the a priori ROIs individually in such a large sample and since standard masks based on existing atlases were mostly large and imprecise, we created spherical masks centered around the peak coordinate of activation. Peak coordinates were collected through a literature search on Pubmed.

Since there was no single study that provided coordinates for all *a priori* regions of interest (ROI), multiple studies were consulted and a list of coordinates was constructed. Subsequently, spheres of 10 mm radius were created around the coordinates (using fslmaths) to produce ROIs of approximately the same size which were large enough to account for interindividual differences and prevent false negatives. When multiple coordinates were found for a single region, the final ROI was selected based on: (1) the specificity (i.e., lack of overlap between different anatomical regions), (2) the nature of the study: meta-analyses were preferred over research articles, and (3) visual inspection which evaluated both accordance with the proposed location presented by Sylvester et al. (2012) and overlap with the relevant Brodmann areas. The coordinates of the FPN originated from the study of Dosenbach et al. (2007) who applied graph theory to resting state functional connectivity MRI data. The coordinates of the CON were collected from a resting state MRI paradigm (Raichle 2011). For the VAN, we consulted an ALE meta-analysis of functional studies using attention and working memory tasks (Kollndorfer et al. 2013) as well as a meta-analysis on visual oddball effects (Kim 2014). Finally, the coordinates of the DMN were based on three studies: the resting state MRI study from Raichle (2011), a resting state PET study (Drevets et al. 1997), and a resting state functional MRI study (Greicius et al. 2003). The final selection of coordinates was transformed from standard space to native space where they could be used as a basis for probabilistic fibertracking. The transformation matrices were created by registering the native image to the standard by use of linear (FSL FLIRT; Jenkinson et al. 2002) and non-linear (FNIRT; Andersson et al. 2007; Jenkinson et al. 2012) transformations and subsequently reversing the transformation matrix (by use of the FSL invwarp command). In subcortical areas, such as the amygdala, it is difficult to

construct accurate standard masks. Therefore, individual amygdala masks were created with FSL FIRST (Patenaude et al. 2011). FSL FIRST uses learned models (based on manually segmented images) to search for the most probable shape of a subcortical structure given the observed intensities in the T1-weighted image of a participant.

Analysis of diffusion MRI

The HCP diffusion data used in this study had already undergone preprocessing by the Wu-Minn consortium (Andersson et al. 2003; Andersson et al. 2012): the b0 image intensity was normalized across runs; EPI distortions, eddy-current-induced distortions, and subject motion were removed; gradient-nonlinearities were corrected; and the diffusion data were registered with the structural image, brought into 1.25 mm structural space, and masked with the final brain mask. Preprocessing was performed using the FSL software (TOPUP, EDDY, and FLIRT tools; Jenkinson et al. 2012), further information on the preprocessing of the diffusion data can be found on the HCP website (http://www.humanconnectome.org/documentation/).

Diffusion parameters were calculated from the preprocessed data using the FSL-tool BedpostX (Behrens et al. 2007; Jbabdi et al. 2012). This tool uses Markov Chain Monte Carlo sampling to calculate the dominant fiber distributions in each voxel. In this dataset, three fiber distributions could be calculated per voxel. Subsequently, the FSL ProbtrackX-tool was used to calculate the tracts between the different regions of interest (Behrens et al. 2007). In accordance with the standard FSL DTI pipeline, 5000 samples were sent from each voxel in the seed region and a curvature threshold of 0.2 and step length of 0.5 mm was used. Furthermore, a midline exclusion mask was used when tracking within the networks since we did not

have hypotheses regarding interhemispheric connectivity. Tracking was done in both directions (from A to B and from B to A) and subsequently averaged to increase the reliability of the tract between the two regions of interest (Clewett et al. 2014). The FSL DTIFIT tool was used to calculate FA, which is a good measure of WM integrity (e.g., Teipel et al. 2010). All brain analyses were performed on the high performance cluster of Ghent University because of the high computational demands of these analyses when performed on the high-quality HCP dataset.

The results of the fibertracking were thresholded to reduce the chances that sporadic/erroneous connection paths drive the findings. Since there is no consensus about the optimal threshold, a relative threshold of 15% of the maximum value was used to account for individual differences as well as be stringent enough to optimize tract quality (see also Bennett et al. 2011; Nakamae et al. 2014; Khalsa et al. 2013). This thresholded path was subsequently used to mask the whole-brain FA image and the mean FA within each tract was calculated. Additionally, tract volume (in voxels) and connection probability (the number of streamlines or connections that connect the seed and the target regions) were calculated. While we are aware that these two measures might suffer from some limitations (Jones et al. 2013), the debate on the effectiveness of the different indices of white matter integrity is still ongoing and both connection probability and tract volume have been used in previous research with interesting results (e.g., Khalsa et al. 2013; Budisavljevic et al. 2016). Consequently, in the present study we used three parameters of interest that have been reported to represent different measures of white matter integrity (Peeva et al. 2013): 1) mean tract FA (representing WM directionality), 2) connection probability (i.e., WM connection strength between two regions), and 3) tract volume.

Statistical analysis

Unix-based scripts were executed on the high performance cluster to calculate and extract the mean FA, connection probability, and tract volume from all participants. The output was written in text files and consequently imported into SPSS (version 20, IBM, Chicago, IL, USA), together with the demographic information, for statistical analysis. Linear regression was performed to assess whether anxiety-depression could predict the integrity of the tracts connecting the key regions of the four neural networks with one another and the amygdala. A laterality effect was only expected in the VAN and therefore, the results of the left and right hemisphere were averaged for all other networks. The model consisted of the ASR anxiety-depression scores as our main independent variable of interest. In addition, other important factors that might influence brain connectivity were added as regressors, i.e., age, gender, ethnicity, intelligence, and intracranial volume (e.g., Clayden et al. 2012). Ethnicity was represented by 5 variables with a value of 0 or 1, as the 6th is redundant (since the majority of participants had a white ethnic background, this predictor was left out). Since ASR anxiety-depression correlated with whole-brain FA (r = -.16, p < .001) and we were only interested in network effects, whole-brain FA was added as an independent variable in the regression analysis. Finally, for the pathways between the amygdala and cortical structures, amygdala size was also added as predictor. Amygdala volume significantly correlated with intracranial volume (r(483) = .55, p < .001). Data were screened for influential cases to prevent the results from being driven by a small subsample of (clinical) participants. For each regression influential cases were defined as having a Cook's distance higher than 4/n (Bollen and Jackman 1990) and excluded from further analysis. Subsequently, outliers (over 3 SD from the mean of the dependent variable)

were removed. We controlled for multiple comparisons (i.e., multiple ROIs) by adjusting the significant p-values for the anxiety variable using the step-down Finner procedure ($p<.05$ corrected, Finner 1990, 1993). Effect size for the regressions was Cohen's f^2.

Results

Regional fractional anisotropy (FA)

Higher anxiety-depression predicted lower FA in the tracts between the amygdala and key regions of the CON, DMN, and FPN. Specifically, greater symptoms relate to lower FA in the tracts between the amygdala and the dorsolateral PFC (dlPFC) within the FPN (β = -.12, $t(440)$ = -3.11, corrected p = .01, R^2 = .30, f^2 = .43), the anterior PFC within the CON (β = -.09, $t(439)$ = -2.28, corrected p = .05, R^2 = .30, f^2 = .43), and the parahippocampal gyrus (PHG) within the DMN (β = -.10, $t(467)$ = -2.62, corrected p < .03, R^2 = .41, f^2 = .69) (Table 3). Figure 1 (left pane) provides a visual representation of the tracts between the amygdala and PFC.

Connection probability

The connection probability analyses also suggested that there was a negative influence of anxiety-depression on the connections between the amygdala and FPN. However, in this case the amygdala – inferior parietal lobe (IPL) tract showed a negative relationship with increasing symptoms (β = -.10, $t(445)$ = -2.11, corrected p = .05, R^2 = .13, f^2 = .15; Table 4). Furthermore, anxiety-depression also predicted the connection probability of the amygdala and the temporal-parietal junction (TPJ) of the VAN (β = -.09, $t(443)$ = -2.03, corrected p = .05, R^2 = .15, f^2 = .18; Table 4). Interestingly however, these two tracts appear to share a lot of voxels (Figure 1, right pane).

Tract volume

Greater symptoms of anxiety and depression were negatively associated with tract volume in the amygdala – dlPFC tract of the FPN (β = -.10, t(439) = -2.14, corrected p = .05, R^2 = .17, f^2 = .20; Figure 1; Table 5). No other effects were significant.

Discussion

This study examined to what extent trait anxiety-depression is represented in the WM integrity within core cognitive-affective networks and between these networks and the amygdala in a large healthy sample. Two main findings pertinent to the central hypotheses emerged. First, WM connectivity between the amygdala and the core networks was significantly affected by anxiety-depression. Specifically, higher anxiety-depression predicted lower WM integrity in the amygdala connections of all 4 different networks although we had expected heightened connectivity between the amygdala and FPN and VAN but lower connectivity between CON and DMN. In both anxiety and depression disrupted emotion-cognition interactions have been reported (Banich et al. 2009), which is in accordance with the present results showing less WM integrity between a major “affective hub” of the brain and cognitive control regions. Second, against expectations, the current study did not detect altered WM integrity among structures of the four networks.

As predicted, anxiety-depression influenced amygdala connectivity to various networks involved in cognitive-affective function. Most interestingly, both key regions (dlPFC and IPL) of the FPN showed reduced amygdala connectivity in relation to anxiety-depression. The dlPFC – amygdala tract was characterized by reduced FA and reduced tract volume while the IPL displayed lower connection probability with the amygdala with increasing symptoms. The dlPFC – amygdala tract has received

most attention in previous research on anxiety, nevertheless with rather mixed outcomes (e.g., Etkin et al. 2009; Eden et al. 2015). While some research reported heightened resting-state functional connectivity between these regions in generalized anxiety disorder (Etkin et al. 2009) others documented lower functional connectivity when viewing fearful faces in social anxiety disorder (Prater et al. 2013). In addition, Eden et al. (2015) did not find an effect of anxiety on the WM integrity of this tract in high trait anxiety. However, self-regulatory control of the FPN such as cognitive reappraisal has been linked to anxiety showing a positive relationship between emotion regulation ability and WM integrity (Eden et al. 2015) but reduced coactivation of the dlPFC during cognitive reappraisal in social anxiety disorder (Goldin et al. 2009). Furthermore, top-down functional connectivity from the dlPFC to the amygdala has been shown to been impaired in depression, indicating that the dlPFC is less effective in exerting cognitive control over the amygdala (Lu et al. 2012). Our findings are broadly consistent with such reports showing reduced structural WM integrity with greater anxiety-depression. An interesting hypothesis would therefore be that this reduction in WM integrity in the amygdala – dlPFC tract contributes to decreased recruitment of dlPFC subregions of the FPN necessary for cognitive control.

With regard to the salience and error detection network (CON), the WM between the anterior PFC (BA 10) and amygdala showed reduced integrity in relation to anxiety-depression. Here, our findings are consistent with reduced fronto-limbic connectivity found in generalized anxiety disorder (Etkin et al. 2009), lower functional coupling between amygdala and BA 10 with increasing social phobia severity (Laeger et al. 2014), and weaker functional connectivity between BA 10 and amygdala elicited by negative stimuli with increasing severity of depression and

anxiety in patients with major depression (Friedel et al. 2009). Etkin et al. (2009) speculate that reduced connectivity between the amygdala and the CON might be associated with dysfunctions in the modulation of the autonomic nervous system. This hypothesis receives some indirect support from the neurovisceral integration model, which states that the central autonomic network, the brain network responsible for the regulation of heart rate variability, comprises both prefrontal cortex (including BA 10) and the amygdala (Thayer and Brosschot 2005). However, future studies should directly investigate whether (WM) connectivity between amygdala and CON has implications for the autonomic nervous system. With regard to structural WM connectivity, evidence of an effect of anxiety and depression on anterior PFC – amygdala connections is rare. While lower uncinate fasciculus integrity has been reported in generalized anxiety disorder (Tromp et al. 2012) and major depressive disorder (Taylor et al. 2007; Liu et al. 2016), the present study extends this prior work by showing that individual differences in anxiety-depression in a large healthy cohort impact the specific connections between amygdala and anterior PFC as determined by tractography.

Similar to the frontal networks (FPN and CON), anxiety-depression also influenced amygdala connectivity to posterior networks (VAN) showing lower connection probability between the amygdala and TPJ in relation to anxiety-depression. The TPJ has been implicated in various functions including bottom-up attention processes (Corbetta and Shulman 2002; Carter and Huettel 2013) and social cognition (Carter and Huettel 2013). Bottom-up attention processes are known to be altered in anxiety as shown by a greater attentional bias to anxiety-relevant stimuli (Bar-Haim et al. 2007). A greater attentional bias to fearful stimuli has already been associated with changes in functional TPJ – amygdala coupling in healthy

participants (Carlson et al. 2013). Yet, while Carlson et al. (2013) reported greater functional connectivity between the two regions, the current study observed lower structural WM connectivity with increasing anxiety-depression. It is, however, worth noting that anxiety or depression disposition was not taken into account in this previous work (Carlson et al. 2013). Taken together, few studies have examined TPJ involvement in anxiety and depression to date but the present structural findings, together with much behavioral work (for review see Bar-Haim et al. 2007) suggesting perturbed bottom-up processing of negative stimuli, would mandate future research effort.

Finally, connectivity between the amygdala and the DMN was also disrupted as shown by lower WM integrity in the amygdala – PHG tract with increasing anxiety-depression symptoms. Prior work in small samples of patients documents greater functional connectivity between amygdala and PHG in anxiety (Liao et al. 2010b), while lower positive resting state functional connectivity between these regions has been reported in adolescent depression (Cullen et al. 2014). The PHG – amygdala connection is believed to constitute a crucial aspect of emotion regulation (Ochsner and Gross 2005) and it has been hypothesized that sustained emotion dysregulation could cause grey matter atrophy in the PHG in social anxiety disorder patients (Liao et al. 2011). Therefore, emotion regulation deficits might contribute to less WM connectivity between these structures. Clearly, more work is needed to disambiguate the effect that anxiety and depression might have on PHG structure and connectivity. Likewise, the relevance of the amygdala – PHG connections for emotion regulation deserves further investigation.

In contrast to the WM connections of the amygdala with the respective networks, WM connections within the networks could not be predicted by anxiety-

depression. This finding was unexpected given the support for altered functional activity within these networks (e.g., Sylvester et al. 2012; Liao et al. 2010a; Korgaonkar et al. 2014). Perhaps, the influence of affective disorders on these networks, and the functions they represent, could be driven by altered, decreased connections with the amygdala. The involvement of the amygdala in anxiety and depression has been supported extensively by previous research (e.g., Davis and Whalen 2001) and it shares activation patterns with abundant and functionally heterogonous regions of the brain (e.g., Bzdok et al. 2013). This amounts to a very large potential for the amygdala and its whole-brain WM connections to influence the functioning of brain networks. Hariri and Whalen (2011) indeed argue that the amygdala is very sensitive to different intrinsic and extrinsic factors and that it will use this information to influence the rest of the brain to guide our behavior. Pessoa (2008) goes further, proposing that it is not possible to separate affective and cognitive contributions to cognitive control functions. Therefore, the functions represented by the neural networks of interest in this study, such as attention control, would be rooted in a constant interaction between the network's key regions and the amygdala relaying emotion information. Taken together, previous research and theories support the notion that altered connections between amygdala and the cognitive networks could result in altered functioning of the networks even though within-networks connections are unaffected.

In addition to anxiety-depression, other variables also emerged as significant predictors of tract integrity. First, the effect of amygdala size, which is mainly predictive of connection probability, is inherently related to the method of tracking used in this study. Since 5000 streamlines originated from each voxel of the seed mask, greater amygdala size should result in a higher number of streamlines arriving

at the target region and therefore higher connection probability (see also Eden et al. 2015). Whole-brain FA also significantly predicted local WM integrity. This effect is in line with expectations and indicates that global and local FA were relatively consistent within participants. Finally, gender also predicted WM integrity, with male participants showing lower tract integrity than their female counterparts. While previous research suggests that men mostly have higher FA values than women, some white matter bundles also show greater FA in women as compared to men (e.g. the corpus callosum or fornix; Inano et al. 2011; Kanaan et al. 2014). Likewise, men also have higher whole-brain grey and white matter volume (Ruigrok et al. 2014). However, while the meta-analysis of Ruigrok et al. (2014) shows that the effect of gender displays a very diverse pattern in local grey matter, i.e. that men can have both higher and lower grey matter volume than women depending on the ROI, no localized WM analyses were reported. Taken together, the effect of gender on WM integrity and volume might not be uniform throughout the brain and deserves further research. The current study used three measures of tract integrity: tract FA, connection probability, and tract volume. Previous research suggests that all three measures represent different measures of white matter integrity, respectively WM directionality, WM connection strength between two regions, and tract volume (Peeva et al. 2013). However, the relationship among these three measures requires further enquiry.

This study has some limitations. First of all, in the HCP dataset no clinician-administered inventory for psychopathology was available and therefore the current study used the ASR questionnaire as a measure of anxiety and depression. However, in studies investigating neural correlates of anxiety and depression in a healthy normative sample, as opposed to a clinical sample, self-reported trait

measures are commonly used (e.g., Etkin et al. 2004; Bishop 2009). Moreover, the use of a dimensional measure in a large general population provides much increased power and allows more interpretative strength regarding generalizability (in contrast to a comparison between a small sample with and without anxiety for example). However, the current study does not enable us to disentangle the effects of anxiety and depression given that the ASR problem scales do not have a separate anxiety and depression measure as well as the high correlation between these two symptom clusters. Thus, future research should investigate to what extent anxiety and depression would show distinct deficits in these networks. A second limitation is that changes in neurotransmitter systems might not be captured by diffusion MRI (Eden et al. 2015), and therefore the current results cannot inform on possible alterations in chemical communication between the regions of interest. Additionally, our analysis pipeline cannot account for artifacts originating from physiological noise (Walker et al. 2011; Jones et al. 2013). However, the implemented FSL pipeline is commonly used (e.g., Korgaonkar et al. 2014; Eden et al. 2015; Peeva et al. 2013) and can model three fiber directions per voxel as well as crossing fibers. Furthermore, while head movements can distort diffusion MRI findings (Yendiki et al. 2013), this cannot explain the effect of anxiety-depression in this study since the effects of head motion were removed in data preprocessing. Care has to be taken when interpreting null findings such as the lack of anxiety-related within-network WM changes. Since previous studies on the effect of anxiety on network functioning were mostly performed in small samples of clinically anxious participants (see also Sylvester et al. 2012), it is possible that the current large general population sample did not have the severity or specificity of symptoms to show these within network functional or structural dysfunctions. Furthermore, due to its correlational nature, the data do not

presently allow any causal conclusions as to how anxiety-depression might perturb brain networks. While this study shows that anxiety-depression can predict WM integrity in the connection between the amygdala and certain structures of core brain networks, we can only speculate about the functional implications since we did not examine the relation to behavioral (performance) data. Future studies will need to elucidate relationship between structural WM alterations and functional deficits.

In conclusion, the current study applied probabilistic tractography in a large sample of healthy young adults to show that anxious and depressive feelings can predict WM integrity between four important neural networks and the amygdala. While these deficits could have important implications for emotion-cognition interactions in anxiety and depression, future studies are needed to determine the consequences of these deficits for cognitive-affective functioning and psychopathology.

Tables and figures

Table 1 Overview of key regions of the neural networks compromised in anxiety (as proposed by Sylvester et al. (2012)) and their peak MNI coordinates.

Network	Region	Right hemisphere	Left hemisphere
Fronto-parietal network	Dorsolateral PFC [a]	46/28/31	-44/27/33
	Inferior parietal lobe [a]	54/-44/43	-53/-50/39
Cingulo-opercular network	Anterior insula [b]	41/3/6	-41/3/6
	Dorsal ACC [b]	0/21/36	0/21/36
	Anterior PFC [b]	32/45/30	-35/45/30
Ventral attention network	Ventrolateral PFC [c]	42/19/-1	
	Temporal-parietal junction[d]	57/-40/22	
Default mode network	Subgenual ACC [e]	-2/33/0	-2/33/0
	Parahippocampal gyrus [f]	25/-26/-14	-22/-26/-16
	Lateral parietal cortex [b]	49/-63/30	-46/-66/30
	Precuneus [b]	0/-52/27	0/-52/27

Notes. If the coordinates were reported in Talairach space they were converted to MNI space using FreeSurfer (Fischl 2012). [a] Dosenbach et al. (2007) as reported in Power et al. (2011), [b] Raichle (2011), [c] Kollndorfer et al. (2013), [d] Kim (2014), [e] Drevets et al. (1997), [f] Greicius et al. (2003) as reported in Fair et al. (2008).

Abbreviations: PFC, prefrontal cortex; ACC, anterior cingulate cortex

Table 2 Sample characteristics.

	Mean	Standard deviation	Range
ASR anxiety-depression	5.64	5.33	0-33
Age	29.16	3.46	22-36
Gender (ratio female/male)	286/197		
Ravens progressive matrices: correct responses	16.51	4.81	4-24
Total intracranial volume	1563335.30	183927.26	889589.97-19993448.92
Whole-brain FA	0.26	0.01	0.23-0.30
Amygdala volume	1569.44	230.52	913.09-2409.18

Abbreviations: ASR, Achenbach adult self-report; FA, fractional anisotropy

Table 3 Tract FA values significantly predicted by ASR anxiety-depression. The predictor of interest is presented in bold ($p < .05$, corrected).

	Amygdala – Dorsolateral prefrontal cortex[1]			**Amygdala – Anterior prefrontal cortex[2]**			**Amygdala – Parahippocampal gyrus[3]**		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Constant	.17	.03		.14	.02		.11	.02	
Anxiety-depression	**-.0005**	**.0002**	**-.13***	**-.0003**	**.0001**	**-.09***	**-.0003**	**.0001**	**-.10***
Age	.00004	.0002	.01	.0001	.0002	.02	-.0003	.0002	-.06
Gender	-.02	.002	-.40***	-.01	.002	-.30***	-.01	.002	-.31***
IQ estimate	.0003	.0001	.08	.0001	.0002	.035	.00002	.0001	.01
Intracranial volume	.00	.00	.14*	.00	.00	.12*	-.00	.00	-.04
Wholebrain FA	.74	.09	.35***	.82	.08	.44***	.76	.07	.44***
Amygdala size	.00001	.00001	.08	.00001	.00001	.13*	-.000002	.000006	-.26
Black-African American	-.003	.002	-.06	-.003	.003	-.071	-.006	.002	-.15***
Asian-Pacific	.01	.01	.04	.001	.01	.004	-.004	.004	-.04
Hispanic	-.0001	.003	-.001	.002	.003	.03	.0001	.002	-.002

Multiple ethnicities	.0001	.01	.0005	.00004	.02	.0001	-.01	.006	-.08*
Unknown ethnicity	-.001	.01	-.01	-.01	.01	-.05	-.001	.004	-.01

Note. * $p < .05$, ** $p < .01$, *** $p < .001$; [1] $R^2 = .30$, $F = 15.704$***, $n = 453$; [2] $R^2 = .30$, $F = 15.96$***, $n = 452$; [3] $R^2 = .41$, $F = 27.00$***, $n = 480$

Table 4 Connection probability significantly predicted by ASR anxiety-depression. The predictor of interest is presented in bold (p < .05, corrected).

	Amygdala – inferior parietal lobe[1]			**Amygdala – right temporal-parietal junction [2]**		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Constant	-63185.10	17088.14		-22240.88	11859.60	
Anxiety-depression	**-205.033**	**97.242**	**-.10***	**-139.19**	**68.66**	**-.09***
Age	-20.76	150.25	-.01	-197.17	106.87	-.08ł
Gender	-5234.39	1402.23	-.23***	-3821.90	998.89	-.23***
IQ estimate	130.45	115.94	.05	-5.28	81.29	-.003
Intracranial volume	.0001	.004	.002	-.01	.003	-.13*
Wholebrain FA	255562.92	59625.85	.21***	124411.16	41285.78	.15**
Amygdala size	24.51	5.49	.25***	25.40	3.88	.37***
Black-African American	1091.82	1376.28	.04	773.00	981.03	.04
Asian-Pacific	2371.15	3713.78	.03	-1130.00	3184.84	-.02
Hispanic	-1584.04	1875.64	-.04	-204.615	1348.22	-.01

Multiple ethnicities	-1272.31	6320.59	-.01	-5826.55	4498.94	.06
Unknown ethnicity	2731.41	4281.84	.03	-2902.49	2621.58	-.05

Note. * $p < .05$, ** $p < .01$, *** $p < .001$; [1] $R^2 = .13$, $F = 5.34$***, $n = 458$; [2] $R^2 = .15$, $F = 6.33$***, $n = 456$

Table 5 Tract volume (in voxels) significantly predicted by ASR anxiety-depression. The predictor of interest is presented in bold ($p < .05$, corrected).

	Amygdala – Dorsolateral prefrontal cortex		
Variable	*B*	*SE B*	*β*
Constant	-10089.60	2729.30	
Anxiety-depression	**-33.77**	**15.81**	**-.10***
Age	20.36	24.57	.04
Gender	-919.69	230.80	-.24***
IQ estimate	-5.40	18.55	-.01
Intracranial volume	.004	.001	.36***
Wholebrain FA	44996.45	9470.50	.23***
Amygdala size	2.21	.86	.14*
Black-African American	499.38	228.10	.11*
Asian-Pacific	1190.08	665.618	.08
Hispanic	336.23	303.25	.05
Multiple ethnicities	-1025.35	1745.557	-.03
Unknown ethnicity	-495.32	701.26	-.03

Note. * $p < .05$, ** $p < .01$, *** $p < .001$; $R^2 = .17$, $F = 7.54$, $n = 452$;

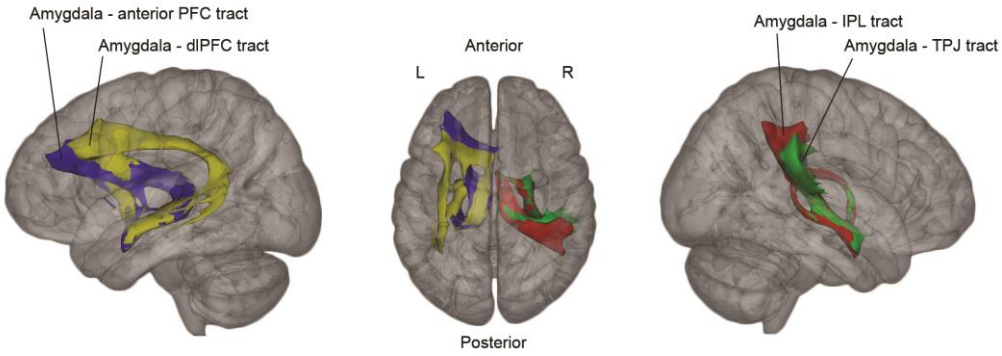

Fig. 1 Visual representation of the tracts from amygdala to dorsolateral prefrontal cortex (dlPFC), anterior prefrontal cortex (PFC), inferior parietal lobe (IPL), and temporal-parietal junction (TPJ). Tracts were thresholded to display the voxels that were present in at least 50% of the sample.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study

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